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Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as Adjunctive Therapy in Advanced Cancer Patients With Chronic Uncontrolled Pain

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ABSTRACT

Context: Prior phase 2/3 studies found that cannabinoids might provide adjunctive analgesia in advanced cancer patients with uncontrolled pain.

Objective: To assess adjunctive nabiximols (Sativex®), an extract of *Cannabis sativa* containing two potentially therapeutic cannabinoids (Δ9-tetrahydrocannabinol [27 mg/mL] and cannabidiol [25mg/mL]), in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.

Methods: Phase 3, double-blind, randomized, placebo-controlled trial in patients with advanced cancer and average pain NRS scores ≥ 4 and ≤ 8 despite optimized opioid therapy. Patients randomized to nabiximols (n=199) or placebo (n=198) self-titrated study medications over a 2-week period, followed by a 3-week treatment period at the titrated dose.

Results: Median percent improvements in average pain NRS score from baseline to end of treatment in the nabiximols and placebo groups were 10.7% versus 4.5% (p=0.0854) in the ITT population (primary variable) and 15.5% versus 6.3% (p=0.0378) in the Per Protocol population. Nabiximols was statistically superior to placebo on two of three quality-of-life instruments at week 3 and on all three at week 5. In exploratory post hoc analyses, US patients, but not patients from the rest of the world (ROW), experienced significant benefits from nabiximols on multiple secondary endpoints. Possible contributing factors to differences in nabiximols efficacy include: 1) the US participants received lower doses of opioids at baseline than the ROW; and 2) the subgroups had different distribution of cancer pain types, which may have been related to differences in pathophysiology of pain. The safety profile of nabiximols was consistent with earlier studies.

Conclusions: Although not superior to placebo on the primary efficacy endpoint, nabiximols had benefits on multiple secondary endpoints, particularly in US patients. Nabiximols might have

utility in patients with advanced cancer who receive a lower opioid dose, such as individuals with early intolerance to opioid therapy.

Keywords

Pain; advanced cancer pain; cannabinoids; nabiximols; opioids; numerical rating scale; randomized control trial.

Running Title

Nabiximols and uncontrolled cancer pain

INTRODUCTION

Cancer-related pain is estimated to occur in up to 60% of patients undergoing anticancer therapy and up to 90% of those with advanced disease (1, 2). In most clinics, treatment of adult cancer pain follows the World Health Organization's three-step ladder for cancer pain relief (3, 4). While this approach is effective in 80–90% of cases, it leaves a sizable percentage of patients, particularly those with advanced disease, suffering from breakthrough and chronic pain, even on Step 3 opioid therapy; moreover, opioid therapy may be associated with serious side effects (5, 6). Thus, a substantial unmet need exists for new analgesics that effectively supplement opioids in cancer patients with chronic pain unalleviated by opioids.

In animal studies, cannabinoids (CBs) have demonstrated synergistic effects with opioids in both chronic and acute pain models (7-10). Among the > 100 CBs present in *Cannabis sativa* L plants, Δ^9-tetrahydrocannabinol (THC) has shown promise in relieving cancer-related pain (11, 12). CBs exert their effects mechanistically through two specific G protein-coupled receptors, CB_1 located predominantly in the central nervous system, and CB_2 expressed primarily in the periphery on immune cells. CBs may also act at other receptors, including G protein-coupled receptor 55 (13), transient receptor potential vanilloid-1 (14), and adenosine receptors (15).

Nabiximols (Sativex®) is an oral mucosal spray formulated from *Cannabis sativa* L extracts and contains THC and cannabidiol in approximately a 1:1 ratio (16), as well as smaller amounts of minor CBs, terpenoids, flavonoids and sterols (17). Two prior randomized double-blind phase 2/3 studies demonstrated that nabiximols had encouraging analgesic effects in advanced cancer patients with pain unalleviated by opioids (18-20). Recently, three similar randomized placebo-controlled trials were conducted to follow up on these encouraging results. Data from two of these trials were reported in a companion publication (21). In brief, across these two studies, 303 patients were randomized to nabiximols and 302 were randomized to placebo

during their parallel-group treatment phases. The primary efficacy endpoints (percent improvement [Study 1] and mean change [Study 2] in average daily pain NRS scores) were not met in either study.

As with any negative results, it is challenging to interpret these unexpected outcomes. To gain further insight, this report analyzes results from the third, nearly-identical phase 3 study. Unlike the previous two studies, the current study found that nabiximols had significant impact on multiple pain and quality-of-life measures. Intriguingly, the beneficial treatment effects were especially pronounced in the subgroup of patients from the US.

METHODS

Ethics

The current study was in compliance with International Conference on Harmonisation Good Clinical Practice guidelines. No trial procedures were performed on trial candidates until written consent had been obtained. The informed consent form, protocol and amendments for the study were approved by the institutional review board or independent ethics committee for each respective trial site or country.

Study Design

The current study (ClinicalTrials.gov identifier: NCT01262651) was a phase 3, double-blind, multicenter, randomized, placebo-controlled trial (**Figure 1**). The design complied with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials II (IMMPACT II) (22). In total, 114 centers participated in Belgium, Bulgaria, the Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the UK, and the US.

Eligible patients had advanced cancer, were ≥ 18 years of age, and had a clinical diagnosis of cancer-related pain that was unalleviated by an optimized maintenance dose of Step 3 opioid therapy. Opioid therapy was considered optimized if: 1) a dose increase was clinically inappropriate due to opioid-related side effects; or 2) further efficacy benefit was not expected at higher doses (for the second definition, patients had to be receiving ≥ 90 mg morphine equivalents/day, inclusive of maintenance and breakthrough opioids). The maintenance opioid was preferably a sustained-release formulation, but an around-the-clock immediate-release formulation was acceptable. To be eligible, patients also had to fulfill the following criteria on each of three consecutive days during the screening period: ≤ 4 opioid break-through analgesic episodes per day (averaged over the three days); a stable maintenance opioid therapy dose; average pain ≥ 4 and ≤ 8 on a 0–10 numerical rating scale (NRS); and average pain scores on

the NRS that did not change by more than 2 points (i.e., no more than a 2-point difference between the highest and lowest scores, with all scores remaining between 4 and 8). Key exclusion criteria included baseline use of morphine at > 500 mg morphine equivalents/day (inclusive of maintenance and breakthrough opioids), current use of more than one type of breakthrough opioid analgesic, planned clinical interventions that would affect pain, and any history of schizophrenia or substance abuse.

Eligible patients were randomized 1:1 to receive nabiximols oral mucosal spray or matching placebo. Treatment was initiated as a single spray in the evening of the first day of treatment and was gradually titrated by one additional spray per day according to a pre-specified dose escalation protocol (**Supplementary Table 1**) until patients experienced unacceptable side effects, experienced acceptable pain relief, or reached the maximum allowed daily dosage of 10 sprays per day. Titration was completed within 14 days, after which patients continued study drug administration at the same dose for another 3 weeks, for a total treatment period of 5 weeks. Whenever possible, stable doses of other prescribed pain medications were continued during the study period. Two weeks after end of treatment, patients were contacted by phone for follow-up safety evaluations.

Efficacy Outcomes

All efficacy assessments occurred during screening, immediately before dosing on Day 1, and 3 weeks (Day 22) and 5 weeks (Day 36) later. The primary endpoint was percent improvement from baseline to end of treatment in average pain NRS score. Key secondary efficacy endpoints included mean change from baseline to end of treatment in the following parameters: average pain NRS score; worst pain NRS score; and sleep disruption NRS score. Other secondary study endpoints included maintenance, breakthrough, and total opioid use per day in morphine equivalents. Primary and key secondary endpoints were derived from patient diary listings reported through an interactive voice response system.

Patients also completed the following questionnaires: Subject Global Impression of Change (SGIC); Patient Satisfaction Questionnaire (PSQ); Physician Global Impression of Change (PGIC); and a constipation NRS.

Safety Analysis

Safety and tolerability were assessed by documenting treatment-emergent adverse events (TEAEs), clinical laboratory tests, and vital sign readings at every patient visit. Patients also completed the Columbia Suicide Severity Rating Scale (C-SSRS) every visit during the treatment period.

Statistical Analysis

All patients who were randomized and received at least one dose of study medication comprised the safety analysis set. All patients in the safety analysis set who had at least one post-randomized efficacy endpoint comprised the intent-to-treat (ITT) analysis set. All patients in the ITT set who had no protocol violations comprised the per-protocol (PP) analysis set.

The primary endpoint and the key secondary endpoints were tested at the level of 0.05 (2-sided), with their Type I error controlled by use of a hierarchical gate-keeping procedure in the following sequence: percent improvement, average pain score, worst pain score, and sleep disruption score. No adjustment for multiplicity was included in analyses for other secondary endpoints.

For the primary efficacy endpoint, i.e., percent improvement in average pain NRS score from baseline to end of treatment, the comparison was analyzed using Wilcoxon rank-sum test. Estimates of the median difference between nabiximols and placebo, together with approximate 95% CI, were calculated using the Hodges-Lehmann approach, and p-values were used for the hierarchical gate-keeping procedure. Other sensitivity analyses for the primary efficacy endpoint included Wilcoxon rank-sum test based on the PP analysis set, Van der Waerden test, and

ANCOVA with the corresponding baseline value as a covariate and treatment group as a factor, based on the ITT analysis set. Mixed-effect Model Repeat Measurement (MMRM) was also applied with baseline NRS average pain score as a covariate, treatment group as fixed factor, the interaction terms for treatment-by-time and baseline-by-time included.

For the key secondary efficacy endpoints (average pain score, worst pain score, and sleep disruption score), ANCOVA was applied, similar to the primary efficacy endpoint analysis. P-values from these analyses were used for the hierarchical gate-keeping procedure. The time course of the treatment effect on the key secondary endpoints was also evaluated in a similar fashion to the primary efficacy endpoint using MMRM on the ITT analysis set. ANOVA was applied on the other secondary endpoints, including PGIC, SGIC or PSQ, daily total/maintenance/break-through opioid dose, except NRS constipation score with ordinal logistic regression.

Subgroup analyses for region (US and ROW) were performed for the primary and key secondary efficacy endpoints using the ITT set at the 0.05 level, without formal adjustment for multiplicity.

RESULTS

Patients

In total, 542 patients were screened for enrollment (**Figure 2**). Of these, 397 fulfilled eligibility criteria and were randomized to nabiximols (n=199) or placebo (n=198). During the subsequent 5-week titration and treatment period, 58 (29.1%) nabiximols patients and 48 (24.2%) placebo patients withdrew from the study. The most common reasons for discontinuation were a TEAE (40 [20.1%] vs. 35 [17.7%] in the nabiximols and placebo groups, respectively) and withdrawal of consent (15 [7.5%] vs.11 [5.6%]). Among those who withdrew due to a TEAE, the most

common reasons were an event related to the underlying cancer (19 [9.5%] vs. 11 [5.6%]) and nausea (5 [2.5%] vs. 2 [1.0%]). Twenty-seven [13.6%] patients died in each treatment group. None of the deaths were treatment-related. Forty-nine deaths were the result of neoplasm progression (25 [12.6%] nabiximols vs. 24 [12.1%] placebo). The remaining two deaths in the nabiximols group were due to pancytopenia and pulmonary embolism, while the remaining 3 deaths in the placebo group were due to pneumonia, gastric perforation and suicide. In total, 141 patients completed the study in the nabiximols group and 150 in the placebo group.

Demographic and baseline characteristics were well balanced (**Table 1**). In both treatment groups, enrollees had an average pain duration of 1.7 years, with an average pain NRS score of 5.6 out of 10 at baseline. Approximately 60% of patients required breakthrough opioid use to manage their cancer-related pain. Mean total daily opioid use at baseline ranged from approximately 186–193 morphine equivalents per day across treatment groups. The distribution and characteristics of the advanced cancers among the enrolled patients are presented in **Supplementary Table 2**.

Study Drug Exposure

The average number of sprays administered per day during the first week of therapy (i.e., during the initial phase of titration) was 3.7 in the nabiximols group and 3.8 in the placebo group. Average daily dosing plateaued and remained stable for the remaining four weeks of treatment, with placebo patients self-administering, on average, one spray more per day than nabiximols patients (7.3 vs. 6.4 sprays per day). Consistent with this, a greater number of patients in the placebo group took more than six sprays per day, on average, over the entire treatment period (115 [58.1%] vs. 79 [39.7%]).

Primary Endpoint

The primary efficacy endpoint was the percent improvement in average pain NRS score from baseline to end of treatment in the ITT population. Using the Wilcoxon rank-sum test as the primary analysis, the percent improvement was calculated as a median difference between groups, where a positive value indicated a treatment difference in favor of nabiximols. Patients had a median percent improvement of 10.7% in the nabiximols group, compared to 4.5% in the placebo group (**Figure 3**), resulting in a treatment difference of 3.41% (95% CI: 0.00%, 8.16%; p=0.0854) (**Table 2**). In the PP population, the median percent improvement was 15.5% and 6.3% (**Figure 3**), resulting in a treatment effect in favor of nabiximols of 5.49% (95% CI: 0.00, 11.11; p=0.0378) (**Table 2**).

Secondary Endpoints

Since the primary efficacy endpoint did not show a significant treatment response in favor of nabiximols, statistical significance was not assessed for the three key secondary endpoints (average pain NRS score, worst pain NRS score, and sleep disruption NRS score), as dictated by the pre-specified hierarchical testing procedures used to control for Type I error. The treatment effects and p-values shown in **Table 2** are therefore unadjusted and are presented for reference only. Results did not differ between nabiximols and placebo for average pain NRS score (p=0.253) or worst pain NRS score (p=0.678), but were in favor of nabiximols for sleep disruption NRS score (p=0.027).

Nabiximols was also associated with greater improvements than placebo in score on the SGIC, PGIC, and PSQ. Treatment effects trended towards improvement at the last visit (p=0.0521, p=0.0861 and p=0.0836, respectively) and favored nabiximols on the SGIC and PSQ at Week 3 (p=0.0024 and p=0.0001), and on the SGIC, PGIC, and PSQ at Week 5 (p=0.0499, p=0.0314, and p=0.0232) (**Table 2**).

Adjunctive nabiximols did not significantly impact daily maintenance opioid dose, break-through opioid dose or total daily opioid dose (p=0.6410, p=0.4217 and p=0.9328, respectively), although, according to protocol, other pain medications including opioids, should have been continued at stable doses. No difference in number of responders based on opioid composite score were observed between treatment groups (odds ratio =1.40; p=0.1063).

US Versus ROW Exploratory Analyses

Of the 397 randomized patients in this study, 129 (32.5%) were recruited in the US and 268 (67.5%) were recruited in the rest of the world (ROW) (**Table 3**). Both groups were almost identical in demographic characteristics with the following notable exceptions: 1) US participants received lower daily dose of opioids at baseline than the ROW subgroup (total daily opioids, 149.1 vs. 209.0 morphine equivalents per day, respectively); and 2) US participants presented with different percentages of cancer pain types. Compared to the ROW, the US group had lower percentages of neuropathic and mixed types of pain, though these differences were not associated with significant baseline differences in average pain NRS scores between US and ROW groups (5.9 ± 1.3 vs. 5.5 ± 1.1, respectively).

In both regional subgroups, nabiximols therapy produced a greater median percent improvement in average pain NRS score than placebo (**Figure 3**). In the US population of the ITT group, the median percent improvement was 8.1% and 1.8% in the nabiximols and placebo groups, respectively (p=0.0839), compared to 12.9% and 6.1% in the ROW population of the ITT group (p=0.4017). The analogous values were 12.3% versus 2.5% (p=0.0191) in the US population of the PP group and 18.5% versus 8.6% (p=0.3902) in the ROW population of the ITT set. Post hoc analyses also indicated a benefit of nabiximols in US patients on multiple secondary endpoints, including mean change in sleep disruption score (p=0.0113), SGIC score (p=0.0053), and PGIC score (p=0.0010) (**Table 4**).

Safety

In total, 144/199 (72.4%) patients on nabiximols and 130/198 (65.7%) on placebo developed one or more TEAE (**Table 5**). The most common in both groups was neoplasm progression (37 [18.6%] vs. 34 [17.2%], respectively), followed by nausea (31 [15.6%] vs. 21 [10.6%]), dizziness (16 [8.0%] vs. 8 [4.0%]), vomiting (16 [8.0%] vs. 13 [6.6%]), and decreased appetite (14 [7.0%] vs. 12 [6.1%])). Overall, 39 (19.5%) patients experienced an event that was mild in severity, 57 (28.6%) experienced a moderate event, and 48 (24.1%) experienced a severe event. The most common severe TEAE in both treatment groups was neoplasm progression (32 [16.1%] vs. 25 [12.6%]). All other severe TEAEs occurred at an incidence of 5% or less.

Treatment-related TEAEs occurred in 70/199 (35.2%) patients in the nabiximols group and 41/198 (20.7%) in the placebo group (**Table 5**). The most common were nausea (17 [8.5%] vs. 10 [5.1%]) and dizziness (15 [7.5%] vs. 5 [2.5%]). All other treatment-related TEAEs occurred at an incidence of < 5% within each treatment group.

In total, 27 (13.6%) patients died in each treatment group. No death was considered treatment-related. Forty-nine of the 54 deaths were attributed to the underlying cancer (25 [12.6%] vs. 24 [12.1]). Two of the remaining five deaths occurred in the nabiximols group, including a patient with metastatic cervical cancer who developed pancytopenia and a patient with metastatic bone cancer who suffered a pulmonary embolism. Other serious TEAEs in the trial were unrelated to study treatment with the exceptions of one case of disorientation and 1 case of visual hallucination in the nabiximols group and one case of vomiting in the placebo group.

No treatment-emergent suicidal behavior in either group was captured by the C-SSRS, and the incidence of treatment-emergent suicidal ideation was roughly equivalent between the two groups. There was one TEAE of completed suicide in a placebo patient, considered unrelated to treatment.

DISCUSSION

Three phase 3 trials have been conducted to assess adjunctive nabiximols in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy. Two of these studies have been published elsewhere (21). This report documents results from the third trial. Nabiximols demonstrated a numerically favorable treatment effect (p=0.0854) on the primary variable (percent improvement in average daily pain NRS scores). Withdrawals for reasons other than disease progression were slightly higher in the nabiximols group compared with the placebo group (26 vs. 22, respectively), and non-imputation analysis using only observed cases showed a treatment effect in favor of nabiximols at Weeks 3 and 5 ($p < 0.05$). In pre-specified analyses of the PP population, the treatment effect favored nabiximols over placebo (p=0.0378) for the primary endpoint.

In accordance with the hierarchical testing procedure, no formal statistical tests of significance were conducted on the key secondary endpoints. Nonetheless, although nabiximols did not improve average pain NRS score (p=0.253) and worst pain NRS score (p=0.678), it improved sleep disruption NRS score (p=0.027). Moreover, ANOVA results favored nabiximols on the SGIC and PSQ at Week 3 (p=0.0024 and p=0.0001), and on the SGIC, PGIC, and PSQ at Week 5 (p=0.0499, p=0.0314, and p=0.0232). Thus, consistent with earlier phase 2/3 studies (18-20), but not with the companion studies (21), nabiximols had beneficial effects in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.

Exploratory post hoc analyses by region revealed that US patients achieved improvement in average pain NRS scores compared with the ROW group in the ITT analysis (p=0.0839) and in the PP population (p=0.0191). Based on these data, we analyzed US patients pooled from the current study and NCT01361607, an identically designed phase 3 study (NCT01361607) that comprises one of the companion studies described in Fallon MT et al. (21) (the third companion

study had no US participants). This pooled analysis identified a treatment effect in favor of nabiximols for the primary endpoint (median difference, 5.07; 95% CI, 0.00–10.39; p=0.0235). In contrast, pooled analysis of ROW patients did not identify a treatment effect for the primary endpoint, and showed a favorable response to placebo in patients older than 65 years of age. In the current study, US patients showed numerically greater improvements in favor of nabiximols relative to ROW patients for all key secondary efficacy measures, and showed similar improvements in the pooled analysis for average pain (p=0.0469), SGIC (p=0.0004), PGIC (p=<0.0001) and PSQ (p=0.0466). Thus, on multiple measures, patients from US study centers responded better to nabiximols than patients from the rest of the world.

Strict eligibility criteria ensured good matching between US and ROW patients and minimized the likelihood that demographics contributed to the different outcomes. Instead, unselected external factors may have been responsible. In this respect, it is noteworthy that baseline opioid use was > 25% lower in the US subgroup than in the ROW subgroup (149.1 vs. 209.0 total morphine equivalents per day, respectively). Additionally, a difference in percentages of cancer pain types between US and ROW participants may have contributed not only to the reduced baseline opioids use in US patients, but also potentially to the differential efficacy of nabiximols in US patients. These observations suggest that nabiximols might possess clinical utility in advanced cancer patients who could benefit from lower Step 3 opioid doses, such as those individuals particularly sensitive to undesirable side effects, which may also be related to cancer type.

In contrast to preclinical studies in which opioid and cannabinoid combination produced antinociceptive synergy (8), nabiximols lacked opioid-sparing effects here and in the companion studies (21). A potential mitigating factor for lack of apparent translation is that the preclinical studies employed drug-naïve rodents, whereas patients in the three clinical trials received chronic high dose opioids. Neither in this study nor in the companion studies did nabiximols

demonstrate an opioid-sparing effect, although the pre-specified requirement that maintenance opioid doses be kept stable across the treatment periods may have limited the likelihood of such a finding.

The safety profile of nabiximols was consistent with previous studies in patients with advanced cancer, and no new safety concerns were identified. The most common all-causality TEAEs were gastrointestinal (nausea and vomiting) and nervous system (dizziness) disorders. The incidence of each of these TEAEs in the nabiximols group was lower in the current study than the earlier phase 2/3 studies (18-20), even when differences in dosing were taken into account. This difference may be due to the current study's use of a longer titration period, with more gradual increments in daily dose. As in earlier studies, most TEAEs in this study were considered mild or moderate in severity. There were 54 treatment-unrelated deaths during the study, most of which were due to the underlying cancer. Notably, the incidence of deaths was much lower in the US than in the ROW population (3.9% vs.18.3%, respectively), although no formal analysis was performed. There was no evidence of abuse or misuse of nabiximols and no reports of treatment-emergent suicidal behaviors or actual suicides in the active treatment group.

In conclusion, this phase 3, randomized placebo-controlled study in advanced cancer patients with chronic uncontrolled pain did not find a positive treatment effect for nabiximols compared to placebo on the primary endpoint (percent change in the average pain NRS score). However, the possibility of positive treatment effects of nabiximols in the subset of US patients cannot be excluded. Further follow-up studies in patients with distinct cancer pain types and taking reduced opioid maintenance doses may be warranted.

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Table 1. Demographics and Baseline Characteristics.

	Nabiximols (n=199)	Placebo (n=198)
Age, mean year (SD)	59.2 (12.0)	60.7 (11.1)
Male, n (%)	111 (55.8)	103 (52.0)
Race, n (%)		
White	185 (93.0)	185 (93.4)
Black	8 (4.0)	10 (5.1)
Asian	0 (0.0)	0 (0.0)
Other [a]	6 (3.0)	3 (1.5)
BMI, mean kg/m^2 (SD)	26.8 (7.6)	26.0 (6.1)
Time since cancer diagnosis, mean year (SD)	3.3 (3.8)	3.3 (3.7)
Type of cancer pain, n (%)		
Neuropathic	26 (13.1)	25 (12.6)
Somatic	10 (5.0)	6 (3.0)
Visceral	26 (13.1)	28 (14.1)
Mixed	96 (48.2)	107 (54.0)
Bone	39 (19.6)	32 (16.2)
Other [a]	2 (1.0)	0 (0.0)
Average pain NRS score, mean (SD) [b]	5.6 (1.2)	5.6 (1.2)
Pain duration, mean year (SD)	1.7 (2.2)	1.7 (2.0)
Use of breakthrough opioid, n (%)	118 (59.3)	126 (63.6)
Daily opioid use, mean morphine equivalents (SD)		
Maintenance	167.5 (118.8)	159.7 (121.2)
Breakthrough	25.4 (38.3)	26.4 (40.4)
Total	192.9 (130.7)	186.1 (131.0)

BMI, body mass index; NRS, numerical rating scale; ROW, rest of world; SD, standard deviation.

a. Other included Hispanic (nabiximols, n=4; placebo, n=1), Hispanic/Latino (placebo, n=1) and black/white (nabiximols, n=2; placebo, n=1).
b. Mean value over the days starting with the first day of the 3-day eligibility period through to the day before the first dose of study medication.

Table 2. Summary of Outcomes.

Primary Efficacy Endpoint [a]	**Estimated Treatment Difference (P-Value)**	**95% CI**
Percent improvement from baseline to the end of treatment in average pain NRS score (ITT)		
Wilcoxon rank-sum test [b]	3.41 (0.0854)♦	0.00, 8.16
ANCOVA [c]	3.00 (0.2543)♦	–2.17, 8.18
MMRM (Week 5) [d]	4.73 (0.1084)♦	–1.05, 10.52
Percent improvement from baseline to the end of treatment in average pain NRS score (PP)		
Wilcoxon rank-sum test [b]	5.49 (0.0378)♦♠	0.00, 11.11
Secondary Efficacy Endpoints [a, e]	**Estimated Treatment Difference (P-Value)**	**95% CI**
Mean average pain NRS score		
ANCOVA [c]	–0.16 (0.2528)♦	–0.45, 0.12
MMRM (Week 5) [d]	–0.26 (0.1117)♦	–0.57, 0.06
Mean worst pain NRS score		
ANCOVA [c]	–0.06 (0.6779)♦	–0.36, 0.24
MMRM (Week 5) [d]	–0.14 (0.4148)♦	–0.48, 0.20
Mean sleep disruption NRS score		
ANCOVA [c]	–0.34 (0.0274)♦♠	–0.64, –0.04
MMRM (Week 5) [d]	–0.38 (0.0264)♦♠	–0.72, –0.05
Questionnaire Outcomes [a, f]	**Estimated Treatment Difference (P-Value)** [g]	**95% CI**
SGIC score		
Week 3	–0.32 (0.0024)♦♠	–0.53, –0.11
Week 5	–0.25 (0.0499)♦♠	–0.50, 0.00
Last Visit	–0.23 (0.0521)♦	–0.47, 0.00
PGIC score		
Week 3	–0.17 (0.0971)♦♠	–0.38, 0.03
Week 5	–0.29 (0.0314)♦♠	–0.56, –0.03
Last Visit	–0.22 (0.0861)♦	–0.46, 0.03
PSQ score		
Week 3	–0.52 (0.0001)♦♠	–0.78, –0.26
Week 5	–0.34 (0.0232)♦♠	–0.64, –0.05
Last Visit	–0.24 (0.0836)♦	–0.52, 0.03

Impact on Opioid Use [a]	Estimated Treatment Effect (P-Value) [c]	95% CI
Daily Total Opioid Dose [h]	–0.34 (0.9328)♦	–8.26, 7.58
Daily Maintenance Opioid Dose [h]	1.46 (0.6410)	–4.68, 7.60
Daily Break-through Opioid Dose [h]	–1.84 (0.4217)♦	–6.33, 2.66
Constipation NRS Score	–0.18 (0.5099)♦	–0.70, 0.35

ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent to treat; MMRM, mixed-effect model repeated Measure; NRS, numerical rating scale; PGIC, Physician Global Impression of Change; PP, per protocol; PSQ, Patient Satisfaction Questionnaire; SGIC, Subject Global Impression of Change.

♦ Result is numerically in favor of nabiximols.
♠ Result is statistically in favor of nabiximols.

b. Estimate of the median difference between nabiximols and placebo, together with 95% CI, was calculated using the Hodges-Lehmann approach.
c. Treatment difference and 95% CI are derived from ANCOVA model with treatment as factor and baseline value as covariate.
d. Treatment difference and 95% CI are derived from a MMRM with treatment, week and treatment by week interaction as fixed effects; the baseline value and baseline by week interaction as covariates; and week as the time variable for repeated measures.
e. The hierarchical testing procedure adopted to control for Type I error prevented formal statistical significance testing of the key secondary efficacy endpoints on the grounds that the primary endpoint analysis was negative; unadjusted p-values shown are for reference only.
f. No adjustment for multiplicity was included in analyses for the "other" secondary endpoints; multiplicity issues should therefore be allowed for when interpreting the results.
g. Derived from an ANOVA model.
h. Opioid doses are expressed as an oral morphine equivalent in mg.
i. Estimated odds ratio (p-value) obtained from logistic regression, with treatment as a factor in the model.

Table 3. Baseline Characteristics of the US and ROW Subgroups.

	US	ROW
Region, n (%)	129 (32.5)	268 (67.5)
Time since cancer diagnosis, mean year (SD)	3.9 (4.5)	3.0 (3.3)
Type of cancer pain, n (%)		
Neuropathic	10 (7.8)	41 (15.3)
Somatic	6 (4.7)	10 (3.7)
Visceral	26 (20.2)	28 (10.4)
Mixed	54 (41.9)	149 (55.6)
Bone	31 (24.0)	40 (14.9)
Other	2 (1.6)	0 (0.0)
Average pain NRS score, mean (SD)	5.9 (1.3)	5.5 (1.1)
Pain duration, mean year (SD)	2.2 (2.5)	1.4 (1.8)
Use of breakthrough opioids, n (%)	97 (75.2)	147 (54.9)
Opioid dose, morphine equivalents per day (SD)		
Maintenance	118.7 (109.5)	185.2 (118.9)
Breakthrough	30.3 (35.3)	23.8 (41.0)
Total	149.1 (118.2)	209.0 (132.2)

ROW, rest of the world; SD, standard deviation; US, United States.

Table 4. Secondary Endpoints in US Patients Versus Patients From the Rest of the World. Nabiximols and placebo values are least square means.

	US				ROW			
	Nabiximols	**Placebo**	**Estimated Treatment Effect (95% CI)**	**P-Value**	**Nabiximols**	**Placebo**	**Estimated Treatment Effect (95% CI)**	**P-Value**
Mean change in worst pain NRS score [a]	–0.8	–0.6	–0.26 (–0.74, 0.22)	0.2837	–0.9	–0.9	0.03 (–0.35, 0.41)	0.8714
Mean change in sleep disruption NRS score [a]	–1.1	–0.4	–0.72 (–1.28, –0.17)	0.0113	–0.7	–0.5	–0.19 (–0.55, 0.17)	0.3077
SGIC score [b]	3.2	3.7	–0.52 (–0.88, –0.16)	0.0053	3.4	3.5	–0.09 (–0.39, 0.22)	0.5734
PGIC score [b]	3.1	3.8	–0.67 (–1.06, –0.28)	0.0010	3.6	3.5	0.01 (–0.30, 0.33)	0.9304
PSQ score [b]	3.4	3.8	–0.43 (–0.91, 0.05)	0.0817	3.4	3.6	–0.15 (–0.49, 0.19)	0.3951

NRS, numerical rating scale; PGIC, Physician Global Impression of Change; PSQ, Patient Satisfaction Questionnaire; ROW, rest of world; SGIC, Subject Global Impression of Change; US, United States.

a. Change from baseline to end of treatment.

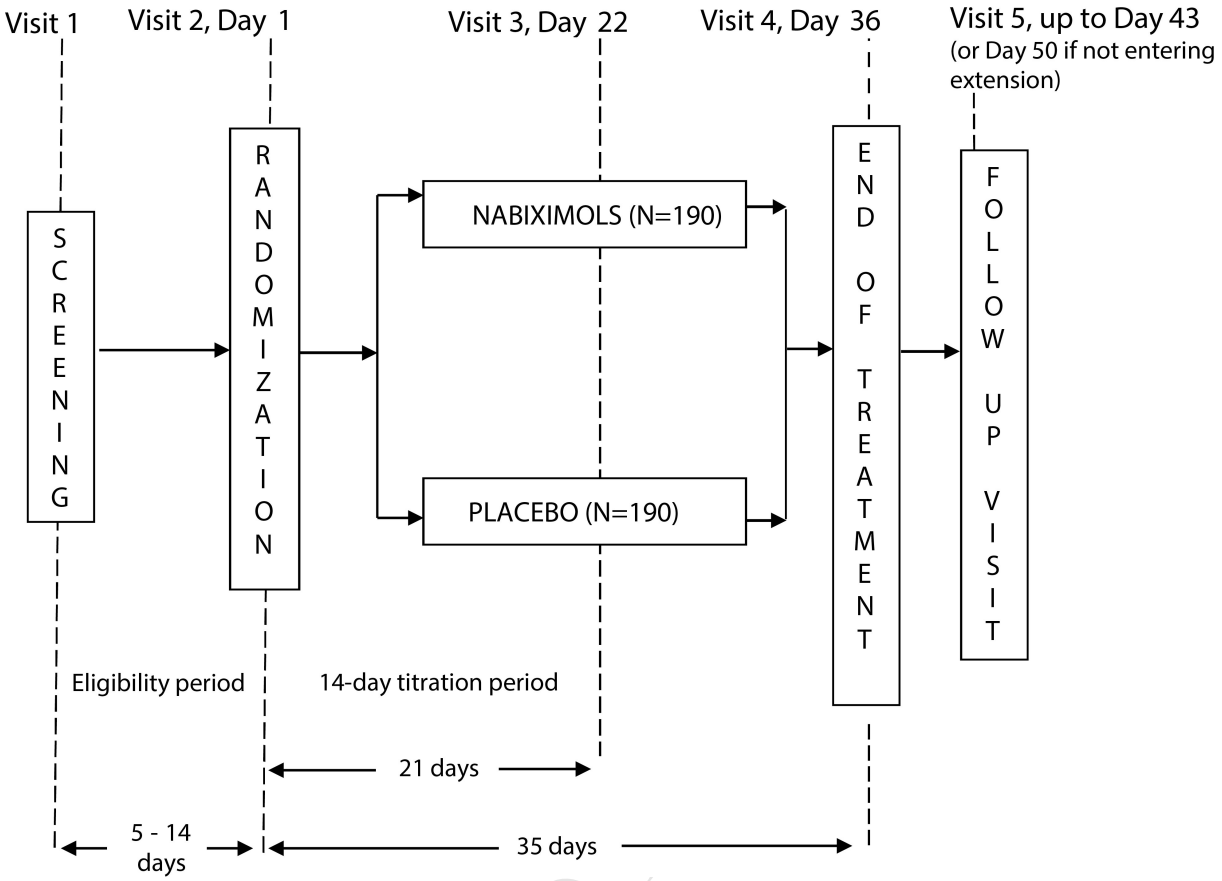
b. Value at last visit.

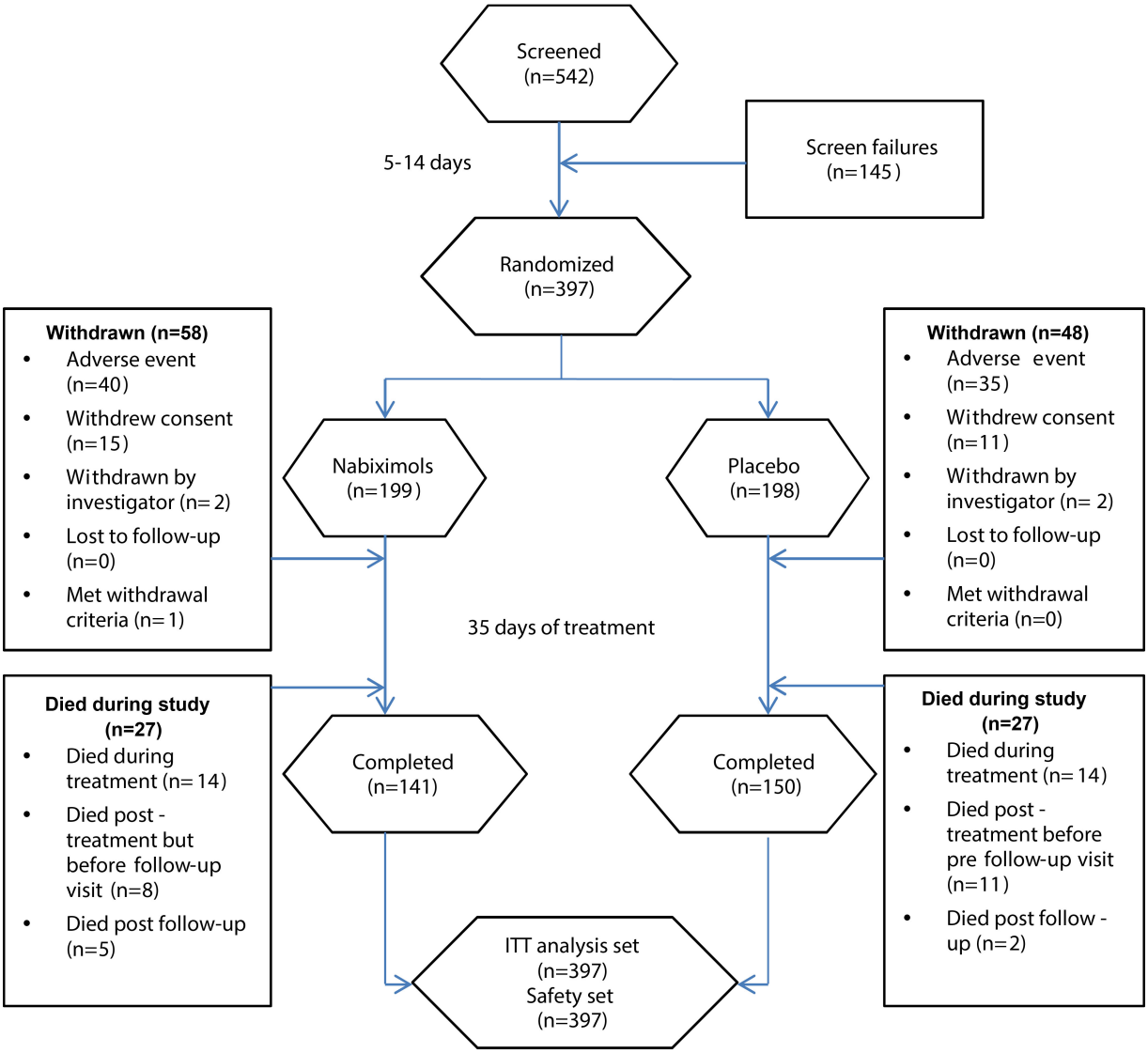
Table 5. Treatment-Emergent Adverse Events in ≥ 5% of Nabiximols Patients.

Event, n (%)	Nabiximols (n=199)	Placebo (n=198)
All causality		
Total [a]	144 (72.4)	130 (65.7)
Neoplasm progression	37 (18.6)	34 (17.2)
Nausea	31 (15.6)	21 (10.6)
Vomiting	16 (8.0)	13 (6.6)
Dizziness	16 (8.0)	8 (4.0)
Decreased appetite	14 (7.0)	12 (6.1)
Fatigue	12 (6.0)	10 (5.1)
Constipation	11 (5.5)	13 (6.6)
Treatment-related [b]		
Total [a]	70 (35.2)	41 (20.7)
Nausea	17 (8.5)	10 (5.1)
Dizziness	15 (7.5)	5 (2.5)

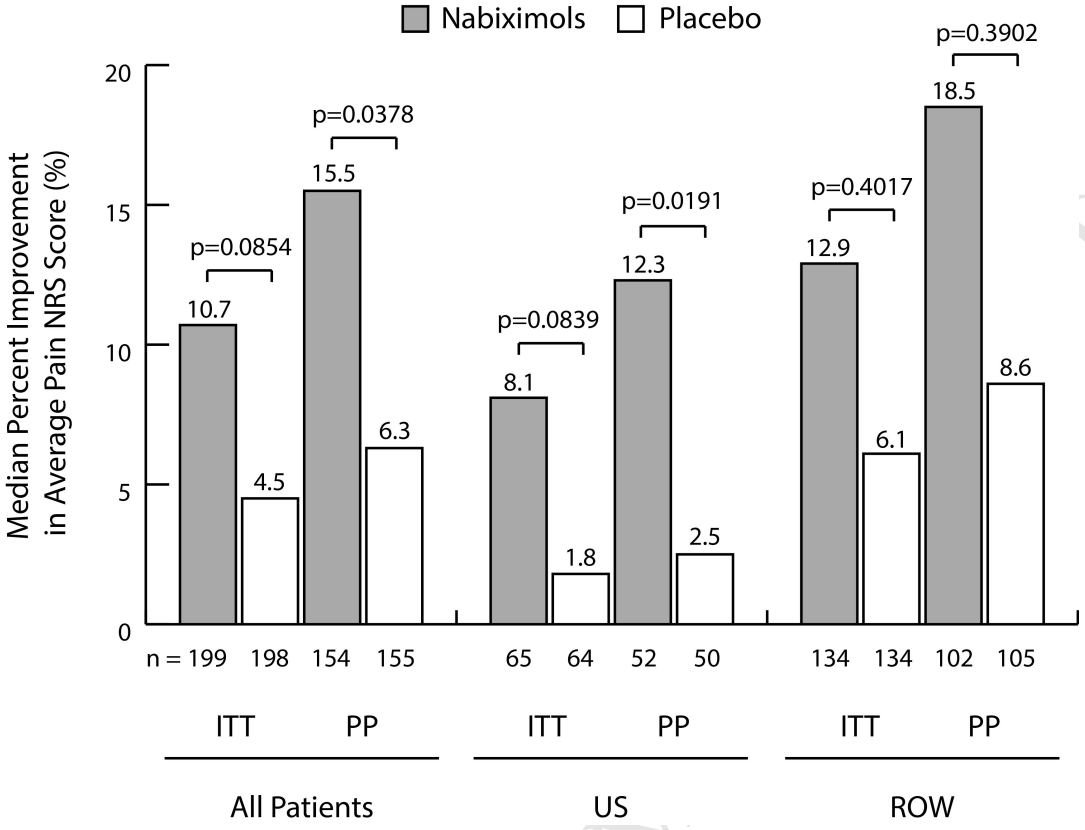
a. Patients with adverse events in multiple system organ classes were counted only once towards the total.

b. Treatment-emergent adverse events judged by the Investigator to be at least potentially related to study treatment.


Visit 1
Visit 2, Day 1
Visit 3, Day 22
Visit 4, Day 36
Visit 5, up to Day 43
(or Day 50 if not entering extension)
SCREENING
RANDOMIZATION
NABIXIMOLS (N=190)
PLACEBO (N=190)
END OF TREATMENT
FOLLOW UP VISIT
Eligibility period
14-day titration period
21 days
5 - 14 days
35 days



ITT = Intention to treat.



Supplementary Table 1. Dose Escalation Protocol.

Day	Number of Morning Sprays	Number of Evening Sprays	Total Sprays Per Day
1	0	1	1
2	1	1	2
3	1	2	3
4	1	3	4
5	2	3	5
6	2	4	6
7	2	5	7
8	3	5	8
9	3	6	9
10	3	7	10

Supplementary Table 2. Baseline Cancer Characteristics.

	Nabiximols (n=199)	Placebo (n=198)	Total (N=397)
Type, n (%)			
Breast	30 (15.1)	32 (16.2)	62 (15.6)
Colon	17 (8.5)	26 (13.1)	43 (10.8)
Esophagus	3 (1.5)	2 (1.0)	5 (1.3)
Gallbladder	1 (0.5)	0 (0.0)	1 (0.3)
Liver	1 (0.5)	2 (1.0)	3 (0.8)
Pancreas	15 (7.5)	8 (4.0)	23 (5.8)
Stomach	3 (1.5)	5 (2.5)	8 (2.0)
Other gastrointestinal	1 (0.5)	5 (2.5)	6 (1.5)
Prostate	18 (9)	21 (10.6)	39 (9.8)
Lung	34 (17.1)	33 (16.7)	67 (16.9)
Bladder	5 (2.5)	4 (2.0)	9 (2.3)
Brain	1 (0.5)	2 (1.0)	3 (0.8)
Chest	0 (0.0)	0 (0.0)	0 (0.0)
Eye	0 (0.0)	0 (0.0)	0 (0.0)
Cervix	4 (2.0)	5 (2.5)	9 (2.3)
Ovary	3 (1.5)	5 (2.5)	8 (2.0)
Uterus	3 (1.5)	5 (2.5)	8 (2.0)
Other genitourinary	8 (4.0)	1 (0.5)	9 (2.3)
Head and Neck	14 (7.0)	8 (4.0)	22 (5.5)
Thyroid	4 (2.0)	2 (1.0)	6 (1.5)
Hematologic	14 (7.0)	10 (5.1)	24 (6.0)
Kidney	6 (3.0)	9 (4.5)	15 (3.8)
Lymphoma	3 (1.5)	1 (0.5)	4 (1.0)
Musculoskeletal	3 (1.5)	1 (0.5)	4 (1.0)
CNS	2 (1.0)	0 (0.0)	2 (0.5)
Skin	3 (1.5)	2 (1.0)	5 (1.3)
Soft Tissue	0 (0.0)	2 (1.0)	2 (0.5)
Other	3 (1.5)	7 (3.5)	10 (0.5)
Histology, n (%)			
Adenocarcinoma	89 (44.7)	112 (56.6)	201 (50.6)
Adenosquamous carcinoma	0 (0.0)	1 (0.5)	1 (0.3)
Glioma	1 (0.5)	1 (0.5)	2 (0.5)
Leukemia	5 (2.5)	2 (1.0)	7 (1.8)

	Nabiximols (n=199)	Placebo (n=198)	Total (N=397)
Lymphoma	3 (1.5)	3 (1.5)	6 (1.5)
Melanoma	3 (1.5)	3 (1.5)	6 (1.5)
Mesothelioma	0 (0.0)	1 (0.5)	1 (0.3)
Myeloma	8 (4.0)	7 (3.5)	15 (3.8)
Neuroendocrine carcinoma	4 (2.0)	3 (1.5)	7 (1.8)
Sarcoma	5 (2.5)	1 (0.5)	6 (1.5)
Squamous carcinomas	22 (11.1)	14 (7.1)	36 (9.1)
Transitional cell carcinoma	1 (0.5)	1 (0.5)	2 (0.5)
Other	58 (29.1)	47 (23.7)	105 (26.4)
Missing	0 (0.0)	2 (1.0)	2 (0.5)